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(54) Title: USE OF A COMPOUND IN THE TREATMENT OF SLEEP DISORDERS AND THE LIKE, IN PROVIDING REFRESHEDNESS ON WAKING AND A METHOD FOR THE TREATMENT OF GROGGINESS THEREWITH

(57) Abstract: There is disclosed the use of triprolidine for enabling an individual to wake refreshed after sleep and the method of treating such an individual with triprolidine. Use of triprolidine as active ingredient in the manufacture of a composition for the treatment of sleep disorders is also described. A method of treating sleep of a person suffering from a sleep disorder, which method comprises administration of an effective dose of triprolidine as active ingredient to such a person is also described. The triprolidine is administered shortly before a person wishes to fall asleep, preferably orally and most commonly in the form of a tablet containing up to 20 mg, e.g. 0.1 mg, 1.25 mg or 2.5 mg, of the active ingredient. The triprolidine is also effective in enabling an individual to sleep more easily.

USE OF A COMPOUND IN THE TREATMENT OF SLEEP DISORDERS AND THE LIKE, IN PROVIDING REFRESHEDNESS ON WAKING AND A METHOD FOR THE TREATMENT OF GROGGINESS THEREWITH

The invention relates to a novel use of a known compound, in particular to the use of that compound in the treatment of sleep disorders experienced by a person, whatever the cause of those disorders

The present invention also relates to a method for the treatment or prevention of grogginess, drowsiness or lethargy on waking from sleep, to the use of triprolidine as an aid to waking refreshed and to the use of triprolidine as both a sleep aid and a means to wake refreshed thereafter.

Although much is known about the use of various pharmaceutical sleeping formulations as aids to sleeping, little has been published about the possibility of a sleep aid enabling an individual to wake refreshed as opposed to merely experiencing degrees of hangover effects such as grogginess, drowsiness, lethargy, etc.

Many people experience, either on an occasional or chronic basis, difficulty in achieving a satisfactory amount of sleep. Such a problem may be attributable to external factors, such as factors causing stress or anxiety, to excessive use or misuse of stimulants (such as caffeine) or depressants (e.g. alcohol), or to temporary disturbance of the person's lifestyle, e.g. occasioned by shift-working or long-haul travel through different timezones. Difficulty in sleeping may also be caused by chronic pain, e.g. pain caused by sciatica etc. Whatever the cause, the condition may be generally considered to be a sleep disorder and may commonly be referred to as "insomnia". It may manifest as difficulty in falling asleep and/or wakefulness during the desired period of sleep, leading to a shortened duration of sleep and/or disruption of the normal pattern of sleep.

The result of these difficulties will commonly be fatigue during the period of wakefulness, which may itself lead to stress and exacerbate the problem.

Various products are available to assist a user in overcoming problems of the type described above. Such products, commonly called "sleeping pills" may, however,

suffer from disadvantageous side-effects. For example, while the products may be effective in sending a user to sleep, their effect may be of short duration, resulting in premature wakening. In other cases, the user may achieve the desired length of sleep but may awake with feelings of grogginess (a "hangover" effect). Such products may also be addictive. Tolerance may also develop to the drug which results in a decrease in effectiveness.

In other circumstances, a person may not suffer from sleep disorders as such, but may simply wish to achieve a particularly good night's sleep. In other words, the use of such products may be elective, rather than necessitated by a clinical need.

In addition to this well documented problem, many people also experience difficulties on waking such as grogginess, lethargy and drowsiness; difficulty in becoming fully alert and an absence of feeling refreshed. These phenomena are not necessarily linked to the number of hours sleep or always encountered as a result of drugs taken prior to sleep such as alcohol, medication, etc. Furthermore, individuals encountering tiredness during waking hours and other individuals having difficulty with insomnia resort to sleep aids in an attempt to increase or improve sleeptime rest. Nevertheless, it is also well documented that a negative side effect of sleep aids can also be an increased feeling of grogginess on waking.

Triprolidine, (E)-2-[1-(4-methylphenyl-3-(1-pyrrolidinyl)-1-propenyl]pyridine, is a first generation anti-histamine and has been marketed alone and, in combination with pseudoephedrine (a decongestant), for the treatment of allergic rhinitis. Triprolidine is known to have sedative effects and has been shown to have an adverse effect on the cognitive functions of users. These are undesirable side-effects for an anti-histamine and may account for the limited extent to which triprolidine has been used in clinical practice. More recently-developed, second generation anti-histamines are less prone to such side effects, and most recent studies involving triprolidine have used that compound as a positive control against which the more modern anti-histamine compounds have been compared. Such studies have generally been conducted using healthy volunteers following day time dosing, rather than persons suffering from any form of sleep disorder, and have been concerned with the effects of the drug on day-time performance.

One study is known to have investigated the effect of triprolidine (amongst other anti-histamines) on sleep directly (*Nicolson et al, Neuropharmacology (1985) 24, 3, 245-250*). In that study single doses of triprolidine (10mg or 20mg sustained release) were given at bedtime to volunteers. It was found that triprolidine did not significantly alter "sleep onset latency" (i.e. the time required to fall asleep) compared with placebo. It was also found that, compared with placebo, triprolidine had no effect on wakefulness during sleep or total sleep time.

It has now been found that, contrary to what might have been expected in the light of previous studies, triprolidine can be used for inducing, prolonging or enhancing sleep, and that its use is accompanied by important benefits in comparison with other compounds known for this purpose that could not have been predicted.

It has also been found that triprolidine surprisingly increases the level of refreshedness felt upon waking if taken before sleeping. Advantageously, this effect is observed whilst triprolidine also acts as a sleep aid in facilitating the onset of stage I sleep and whilst enhancing sleep.

The increased level of refreshedness felt upon waking after taking triprolidine prior to sleeping was not expected and there has been no known disclosure of such an effect previously encountered.

According to a first aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof as active ingredient of an aid to waking refreshed after sleeping.

According to a second aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a composition for enabling an individual to wake refreshed after sleeping.

According to a third aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for enabling an individual to wake refreshed after sleeping.

According to a fourth aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof in the preparation of a sleep aid which also enables an individual to wake refreshed after sleeping.

According to a fifth aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof as active ingredient of a sleep aid which also enables an individual to wake refreshed after sleeping.

According to a sixth aspect of the present invention there is provided the use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for the treatment or prevention of a sleep disorder which also enables an individual to wake refreshed after sleeping.

According to a seventh aspect of the present invention there is provided a method for the treatment or prevention of grogginess, drowsiness or lethargy on waking from sleep in a mammal comprising the administration to the mammal in need thereof of a non-toxic effective dose of triprolidine or a salt or hydrate thereof prior to the desired sleeping time.

According to an eighth aspect of the present invention there is provided a method for enabling an individual to wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

According to a ninth aspect of the present invention there is provided a method for aiding an individual's sleep and for also enabling the individual to subsequently wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

According to a tenth aspect of the present invention there is provided a waking refreshed aid comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to an eleventh aspect of the present invention there is provided a pharmaceutical formulation for the treatment or prevention of grogginess, drowsiness or lethargy on waking after sleeping, comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to a twelfth aspect of the present invention there is provided a pharmaceutical formulation for enabling an individual to wake more refreshed after sleeping, comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to a thirteenth aspect of the present invention there is provided a method of treating sleep of a person suffering from a sleep disorder, which method comprises administration of an effective dose of triprolidine as active ingredient to such a person.

According to a fourteenth aspect of the present invention, there is provided the use of triprolidine as active ingredient in the manufacture of a composition for the treatment of sleep disorders.

According to a fifteenth aspect of the invention, there is provided a method for inducing, prolonging and/or enhancing sleep, which method comprises administration of an effective dose of triprolidine as active ingredient to a person desirous of achieving sleep.

In a related aspect of the invention, there is provided the use of triprolidine as active ingredient in the manufacture of a composition for inducing, prolonging and/or enhancing sleep.

It will also be understood that the term "inducing, prolonging and/or enhancing sleep" may encompass the treatment of a sleep disorder, i.e. a difficulty in achieving satisfactory sleep due to some internal or external factor, e.g. pain, stress or anxiety, misuse of stimulants or depressants, or temporary disturbance of lifestyle. Alternatively, it may encompass elective desires on the part of a user to achieve a

particularly beneficial period of sleep. Such a desire may, for instance, arise in anticipation of important events the following day for which a person may wish to be fully alert and refreshed. In any event, the term "sleep disorder" as used herein should be taken to independently include any one or more of the foregoing and, specifically, any objective or subjective difficulty in an individual in any one or more of the following:-

- getting to sleep, especially stage 1 sleep
- staying asleep
- sleeping well
- waking refreshed
- waking alert
- keeping awake
- keeping alert
- keeping refreshed
- performing well the next day

The present invention also extends to the use of triprolidine as a sleep aid. By definition, a sleep aid extends to use by a healthy individual who elects for a sleep aid, for example, before an important event. The term "sleep aid" as used herein includes any one or more of the following benefits:-

- faster onset to stage 1 sleep
- increasing duration of sleep periods
- decreasing the number and duration of awakenings
- increasing total duration of sleep
- increasing probability of sleeping well
- improving insomnia, especially chronic or mild-moderate insomnia
- decreasing disturbances during sleeptime
- improving quality of sleep,
- as determined by any standard or known subjective or objective measures, for instance the Karolinska scale, Loughborough sleep log or actimetry.

The method of aiding an individual's sleep typically indicates aiding in the sense of providing any one or more of the above mentioned benefits.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, wake refreshed after sleeping is in the range 1-100%, more typically, 5-70%, most typically 10-35%. An especially typical range as aforesaid is 15-30% or even more especially 20-30%. Typically, by the terms "waking refreshed" or "wake refreshed" is meant that an individual felt at least refreshed on waking, preferably, the terms are defined as the individual felt very refreshed or refreshed in accordance with the Loughborough sleep log.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, wake refreshed after sleeping is more than 2%, more typically, more than 8% and most typically, more than 15%. An especially typical level as aforesaid is more than 18% or even more especially more than 20%.

By the term sleeping as referred to herein is meant an individual in at least Stage I sleep. By the term sleeptime as referred to herein is meant the time an individual desires to go to sleep.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt alert after sleeping is in the range 1-100%, more typically, 5-60%, most typically 10-30%. An especially typical range as aforesaid is 15-30% or even more especially 20-30%.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt alert after sleeping is more than 2%, more typically, more than 8%, most typically more than 12%. An especially typical level as aforesaid is more than 16%.

By the term felt alert is meant that an individual felt at least alert on waking. Preferably, the term is defined as the individual felt alert, very alert or extremely alert in accordance with the Karolinska 9-point scale.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt sleepy on waking is less than 25%, more typically, less than 20%, most

typically less than 15%. An especially typical level as aforesaid is less than 14% or even more especially a mean level of less than 12%.

By the term felt sleepy is meant that an individual felt sleepy on waking. Preferably, the term is defined as the individual felt sleepy or very sleepy in accordance with points 8 or 9 of the Karolinska 9-point scale.

Preferably, in use of the present invention as defined herein, the mean subjective feeling of refreshedness after waking as, for instance, determined on a 5 point scale, e.g.. by the morning log of the Loughborough sleep log, is increased by at least 2%, more typically, by at least 4%, most typically, by at least 5%, as compared with an equivalent dose of placebo.

Typically, in use of the present invention as defined herein, the mean subjective feeling of refreshedness after waking as for instance, determined on a 5 point scale, e.g.. by the morning log of the Loughborough sleep log, is increased by between 1-20%, more typically, 1-15%, most typically 2-10% as compared with an equivalent dose of placebo.

The degree of refreshedness and quality of sleep may be determined by the "morning" log of the Loughborough sleep log with the highest degree of refreshedness or quality of sleep being represented as 1 and the lowest being represented as 5. Accordingly, the percentage increase in refreshedness or quality of sleep is measured in this context by the decrease in the mean refreshedness or quality of sleep.

Preferably, by the use of the present invention, the response of awakening very refreshed or refreshed, as determined, for instance, by the morning log of the Loughborough sleep log, is improved by at least 20 %, more preferably, by at least, 30%, most preferably by at least 40%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of awakening very refreshed or refreshed, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is improved by between 5% and 100%, more typically, by between 10% and 80%, most typically by between 20% and 60%,

especially 40-55% and more especially 40-45% as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of feeling extremely alert, very alert or alert , as determined, for instance, in accordance with the Karolinska 9-point scale, is improved by at least 2%, more preferably, by at least, 5%, most preferably by at least 10%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of feeling extremely alert, very alert or alert, as determined, for instance, in accordance with the Karolinska 9 point scale, is improved by between 1% and 40%, more typically, by between 2% and 30%, most typically by between 10% and 20%, as compared with an equivalent dose of placebo. An especially preferred range is 10-30%.

Preferably, by the use of the present invention, the response of feeling sleepy and needing to make some effort to stay awake or very sleepy, as determined, for instance, in accordance with points 8 and 9 of the Karolinska 9 point scale, is improved (ie. decreased) by at least 2%, more preferably, by at least, 4%, most preferably, by at least 10%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of feeling sleepy and needing to make some effort to stay awake or very sleepy, as determined, for instance, in accordance with points 8 and 9 of the Karolinska 9 point scale is improved (ie. decreased) by between 1% and 100%, more typically, by between 2% and 75%, most typically, by between 4% and 60%, as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, the sleeptime awakenings, as for example determined by the Night diary of the Loughborough sleep log, may be decreased by 2-40%, typically, by 10-35%, most typically by 15-30%, as compared with an equivalent dose of placebo. An especially preferred range is 15-40%. Preferably, in use of the present invention as defined herein, the sleeptime awakenings may be decreased by more than 5%, more preferably by more than 10%, most preferably, by more than 15%, as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, sleep disturbance index (SDI), as for instance determined by actimetry, may be decreased by more than 5%, more preferably by more than 10%, most preferably by more than 15% as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, SDI may be decreased by 5-30%, more typically 5-25%, most typically 10-20 % as compared with an equivalent dose of placebo. An especially preferred range is 10-30%, more especially 10-25%.

Preferably, in use of the present invention as defined herein, time to sleep onset (TTSO) as, for instance, determined by actimetry may be decreased by 5-40%, more typically 15-35%, most typically 20-30% as compared with an equivalent dose of placebo. An especially preferred range is 20-40%, more especially 20-35%.

Preferably, in use of the present invention as defined herein, the time to sleep onset (TTSO) as compared with an equivalent dose of placebo is decreased by at least 10%, more preferably by at least 15%, most preferably, by at least 20%.

Preferably, the quality of sleep experienced as felt after awakening is also improved by the use of the present invention, typically the quality of sleep is improved by 2-30%, more typically 5-30%, most typically 10-20% as compared with an equivalent dose of placebo and as, for instance, determined by the morning log of the Loughborough sleep log. Typically, in use of the present invention as defined herein, the quality of sleep is improved by at least 2%, more preferably at least 5%, most preferably at least 10% as compared with an equivalent dose of placebo.

Preferably, in use of the present invention, the time to fall asleep as determined, for instance, by the Night diary of the Loughborough sleep log is decreased by 1-40%, more typically 5-35%, most typically 10-30%. An especially preferred range is 10-40%, more especially 10-35%. Typically, in use of the present invention as defined here, the time to fall asleep as aforementioned is decreased by at least 2%, more typically, by at least 5%, most typically by at least 10% as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of sleeping extremely well or very well , as determined, for instance, in accordance with the morning log of the Loughborough sleep log, is improved by at least 20%, more preferably, at least, 35%, most preferably at least 50%, as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log, is found for at least 20% of individuals, more preferably, at least 25%, most preferably, at least 30%. For example over 35% of individuals had such a response.

Typically, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is improved by between 10% and 200%, most typically, by between 20% and 150%, more typically by between 25% and 135% as compared with an equivalent dose of placebo. Typically, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is found for between 25% and 100% of individuals, more typically, 30-80% most typically 35-70%. Especially preferred is the response in at least between 35-60%, of individuals, more especially 35-45%.

It will be understood that references herein to "triprolidine" include the compound (E)-2-[1-(4-methylphenyl-3-(1-pyrrolidinyl)-1-propenyl]pyridine as well as salts thereof that are acceptable for administration to the human body. Acid addition salts may particularly be mentioned, including the hydrobromide and hydrochloride salts. The hydrochloride salt, i.e. triprolidine hydrochloride, is particularly preferred for use in accordance with the invention. Solvates of triprolidine, notably hydrates, e.g. monohydrates, and to the extent that triprolidine may exist in polymorphic forms, all such polymorphs are within the scope of the invention.

The term "refreshed" as used herein means an individual waking refreshed or alert after a dose of triprolidine has been administered prior to sleep. In this context, the determination of whether an individual is feeling "refreshed" may be made by a subjective test. An example subjective test is measuring the degree of alertness on,

for instance, the Karolinska scale or the feeling of being refreshed as determined by, for instance, the Loughborough sleep log. Alternatively, refreshedness may be based upon the inverse relationship between refreshedness and relative levels of sleepiness as determined by the Karolinska scale.

By the term individual as referred to herein is meant any mammal or human.

The administration of the active ingredient in accordance with the invention may be beneficial in that there is evidence that users feel more refreshed upon awakening, which is not the case with other treatments for sleep disorders, or indeed in the absence of any treatment, and do not experience grogginess or a "hangover" effect after the required number of hours sleep. This too is surprising in view of the fact that such feelings have been reported in relation to other active ingredients which have a comparable mode of action to that of triprolidine. Furthermore, there is no evidence that repeated use of the active ingredient over the course of several days leads to any loss of effect.

The administration of the active ingredient in accordance with the invention may also be beneficial in that it may decrease the time required for a user to fall asleep, which is surprising in view of the previously-reported studies on volunteers. In addition, the total period of sleep may be increased and the incidence and duration of night-time wakenings experienced by the user may be reduced.

Although the active ingredient may be co-administered with another pharmacologically active agent, presently preferred formulations contain triprolidine as the sole active agent.

The active ingredient is preferably formulated in such a manner as to lead to non-sustained, substantially immediate release of the active ingredient, i.e. the formulation is preferably free of ingredients intended or effective to prolong or sustain release of the active ingredient.

Administration of the active ingredient in accordance with the invention may be by a variety of routes. However, most commonly the active ingredient will be administered orally. An alternative mode of administration may be administration to the mucous

membranes of the nasal passages. Further modes of administration are transdermal (e.g. using transdermal patches or bandages), rectal (e.g. as suppositories), optical, sub-lingual and pulmonary.

For oral administration, the active ingredient may be put up in a variety of dosage forms. Most commonly, the active ingredient will be formulated and administered as a tablet or the like. However, formulation as capsules, lozenges, drinks or as a syrup (solution or suspension) may also be possible, as may other dosage forms such as oral sprays.

For nasal administration, the active ingredient may be formulated as a solution, emulsion or suspension and administered by means of a spray using a suitable delivery device. Alternatively, for pulmonary administration, the active ingredient may be administered as a powder, either from a pressurised aerosol delivery device or from a so-called dry powder inhaler.

For formulation in the presently preferred form, i.e. as a tablet, the active ingredient will generally be combined with various excipients in a manner which is known *per se*. In particular, the tablet will generally comprise one or more diluents or bulking agents. A diluent may also serve as a disintegrant, or the formulation may incorporate a separate disintegrant. A lubricant may also be included to facilitate release of the formed tablets from the tabletting dies of a tablet forming machine.

Thus, according to a further aspect of the invention, there is provided a tablet for enabling an individual to wake refreshed after sleeping, which tablet comprises triprolidine as sole active ingredient in admixture with one or more diluents and/or a disintegrant, the tablet comprising more than 0.01mg and less than 4.9mg triprolidine.

As noted above, the formulation may incorporate one diluent or bulking agent, or more than one. Formulations are preferred which contain blends of two or more diluents, one of which may also serve as a disintegrant.

Preferred materials for the diluent or bulking agents include polysaccharides and derivatives thereof, and saccharides.

Polysaccharides which may be used include starch, e.g. maize starch, cellulose, e.g. powdered cellulose and microcrystalline cellulose, water-insoluble modified starches, e.g. sodium carboxymethyl starch, water-insoluble cellulose derivatives, e.g. croscarmellose sodium (cross-linked sodium carboxymethyl cellulose), cross-linked polyvinylpyrrolidone and alginic acid.

Another preferred form of diluent is a saccharide. Suitable saccharides include, for example, sucrose, lactose, dextrose, sorbitol, mannitol, xylitol and maltodextrin. Lactose and sucrose are preferred saccharides. Lactose is especially preferred. Saccharide diluents may also be beneficial in terms of modifying the taste of the formulation.

Particularly preferred diluents are dicalcium phosphate, microcrystalline cellulose, e.g. the products sold as Avicel PH-101 and Avicel PH-102 (Avicel is a Trade Mark) by the FMC Corporation of Philadelphia, Pa., USA, and lactose.

Another preferred disintegrant is a croscarmellose sodium, for example the product sold as Ac-Di-Sol (Ac-Di-Sol is a Trade Mark) by the FMC Corporation. This product, when included in the formulation, also serves as a disintegrant.

The disintegrant has the effect of causing the tablet composition to disintegrate under the conditions found in the gastro-intestinal tract. Apart from croscarmellose sodium, examples of disintegrants include one or more of wheat starch, maize starch, potato starch, sodium starch glycolate, low-substituted hydroxypropyl cellulose, alginic acid, cross-linked polyvinylpyrrolidone and magnesium aluminium silicate. Preferred disintegrants are those which swell on the action of water thus causing the ingredients in the tablet to be pushed apart and out into the aqueous disintegration medium. The preferred disintegrant is croscarmellose sodium. The disintegrant is present at an effective disintegrating amount, for example up to 25% by weight of the composition, more preferably 1-25% w/w, further preferably 3-20% w/w and most preferably 5-15% by weight of the composition.

Particularly preferred compositions, in a particular tablet compositions, include a blend of a cellulosic diluent, a saccharide diluent and a disintegrant. The preferred cellulosic

diluent is microcrystalline cellulose, the preferred saccharide is lactose and the preferred disintegrant is croscarmellose sodium.

A preferred formulation, in particular a tablet formulation, comprises the cellulosic diluent, the saccharide diluent and the disintegrant in the ratio of 0.01-10 parts by weight of cellulosic diluent, 0.01-10 parts by weight of saccharide diluent to 1 part by weight of disintegrant. More preferably, the formulation contains 2-5 parts by weight of cellulosic diluent per part by weight of disintegrant, and 4 to 7 parts by weight of saccharide diluent per part by weight of disintegrant.

The diluents and/or disintegrant are preferably incorporated into the compositions in finely divided (powder) form.

The diluents and disintegrant preferably together constitute in excess of 80% w/w of the tablet formulation, more preferably in excess of 90% w/w, and most preferably in excess of 94% w/w.

The lubricant may be, for example, stearic acid, a metallic stearate, a polyethylene glycol of molecular weight of 4,000 or more, or purified talc. The preferred lubricant is a metallic stearate, particularly magnesium stearate, which may be present in the formulation at relatively low levels, typically less than 1% or 0.5% by weight.

It has been found to be particularly advantageous for the tablet formulation to be formed with a coating, preferably a sugar coating or film coating process, more preferably a film coating comprising a hydrophilic polymer, particularly a cellulose derivative such as a methylated cellulose derivative, e.g. hydroxyethylmethylcellulose and, particularly, hydroxypropylmethylcellulose.

The coating may also comprise an inorganic filler material, most preferably french chalk, to enhance the physical properties of the coating and prevent cracking etc, and also a pigment, e.g. a titanium dioxide pigment dispersion.

It has been found that, in addition to improving the appearance of the tablet and acting as a barrier to ingress of moisture, the film coating is also effective in masking the taste of the active ingredient.

The tablet formulation may be prepared by a process involving dry blending or wet or dry granulation. However, it is preferred to use a manufacturing method which involves direct compression into a tablet without an intermediate, e.g. a wet or dry granulation, stage.

The formulation may be made by dry mixing the active ingredient with the other ingredients, e.g. the lubricant and diluents and disintegrant, e.g. in a powder blending machine. It is particularly preferred that the active ingredient is dispersed by progressive dilution with agitation in a proportion, e.g. about one-half, of the excipients so as to achieve even distribution of the active ingredient in the excipients, and then to add the remainder of the excipients with further agitation and mixing. The mixture may then be compressed in a tablet forming machine and a coating, preferably a sugar coat or a film coat may then be applied to the tablets so formed by spraying the tablets with a solution or suspension of the coating-forming ingredients while the tablets are tumbled.

Such a direct tablet compression manufacturing method has been found to be beneficial in that it avoids problems attributable to crystal growth and changes in morphology which might occur in a wet granulation process.

Other, currently less preferred, dosage forms may be prepared in a manner which is generally known *per se*. For example, syrups may be prepared by dissolving or suspending the active ingredient in a liquid vehicle, e.g. water, optionally with suspending agents or the like, e.g. cellulose derivatives, gums etc.

For administration by inhalation, via nose or mouth, the formulations may be formulated with a compressed gas or liquified gas propellant, e.g. any conventionally used propellant such as a chlorofluorocarbon, hydrofluorocarbon, compressed hydrocarbon, nitrogen etc. Alternatively, the active ingredient may be formulated as a dry powder, generally in admixture with a diluent such as crystalline lactose.

The amount of active ingredient to be administered in a single dose may vary quite widely, depending *inter alia* on the desired effect and the mode of administration. However, a formulation for oral administration, e.g. a tablet, will generally contain at

least 0.01 and up to 20mg of active ingredient, more commonly at least 0.5mg and less than 10mg of active ingredient, most commonly no more than 5mg, e.g. 1.25 or 2.5mg. Doses of formulations for administration by nasal and sub-lingual administration, which would be expected to deliver the active ingredient more quickly and efficiently, may contain less active ingredient, e.g. between 0.1 and 1.0mg, e.g. about 0.5mg and generally at a level of 20% of the oral dose levels mentioned herein. Preferably, such nasal and sub-lingual formulations contain active ingredient in the range 0.01-2.5mg, more preferably, 0.05-1.0mg and most preferably, 0.1-0.5mg.

In general, the desired dose (which may comprise one or more unit doses, e.g. one or two tablets or the like) will be taken by a user prior to the desired time at which it is desired for the composition to take effect. Most commonly, the dose will be taken at night-time, i.e. prior to the user sleeping through hours of darkness. Typically, the dose may thus be taken after 8pm in the evening or later, say after 9pm or after 10pm. Typically, it may be recommended that the user take the composition between 0 , more commonly 1 minute and 2 hours prior to the time at which he or she wishes to fall asleep. Most commonly, the composition may be taken about 10 to 30 minutes prior to that time. In addition, however, the active ingredient may be effective, particularly at lower doses, in restoring sleep, e.g. in the event of night-time waking.

Preferably, the use of triprolidine in any aspect of the invention as defined herein is its use as active ingredient. Preferably, the triprolidine in any aspect of the invention defined herein is in the form of a non-toxic effective dose, preferably, suitable for any given mammal or human and determined in accordance with age and weight.

Preferably, to obtain the benefits on waking or otherwise as defined herein, the active ingredient of triprolidine administered before sleeptime is less than 10mg, typically less than 5mg, more preferably, less than 4.5mg, most preferably less than 4.0mg. Especially preferred is a dose as aforesaid of less than 3.5mg and most especially preferred is a dose of less than 3.0mg. Typically, the dose of triprolidine is between 0.01 and 10.0mg, preferably, between 0.01 and 4.9mg, more preferably, between 0.1 and 4.5mg, most preferably between 0.5 and 4mg. Especially preferred is a dose of between 1 and 3.5mg and more especially a dose of between 2.0 and 3.0mg. Most especially preferred is a dose as aforesaid of about 2.5mg or 1.25mg. Preferably, the above dosage levels are based on triprolidine hydrochloride monohydrate and

amounts of other salts or hydrates should be varied accordingly to deliver the equivalent amount of active ingredient.

In the formulations of the present invention, the triprolidine may be in any suitable release form such as a slow release , sustained release, immediate release or uncontrolled release form. The formulation may also be in any one or more of the following delivery forms:-

Pastilles
lozenge
chewable tablets
fondant-fill tablets
coated or uncoated tablets
sub-lingual tablets
fast-melt tablets
hot or cold drinks
syrups
drops
emulsions
dry powder
suspension
transdermal patch
suppository
sub-lingual and nasal sprays

Preferably, the dose of the triprolidine in accordance with the invention may be taken by an individual before it is desired to go to sleep (sleeptime), preferably less than two hours before sleeptime, more preferably, less than one hour before sleeptime, most preferably, less than 20 minutes before sleeptime. Especially preferred is to take the dose of triprolidine less than 15 minutes before sleeptime.

Preferably, the dose of triprolidine is less than 4 doses per day (24 hour period), more preferably, less than 3 doses per day, most preferably less than 2 doses per day. Especially, preferred is 1 dose per day.

The packaging of the invention as defined herein may be in any suitable form such as, for example, a blister pack, bottle, tamper-proof container, sachet, box, etc. The packaging of the invention may be associated with instructions for any of the features or preferred features of the invention as defined herein.

For the avoidance of doubt, reference to the "use of the present invention" herein should be taken to include "the method of the invention", and "use of a pharmaceutical formulation" as well as use of the present invention per se.

Advantageously, the use of triprolidine in the present invention results in a reduced hangover or morning grogginess effect as compared with other sleep aids or sleep disorder remedies. More advantageously, the use of triprolidine in the present invention provides an improved degree of refreshedness or more refreshed feeling upon waking as determined by the Loughborough sleep log or Karolinska scale and as compared with placebo.

For the avoidance of doubt, reference to quantities of triprolidine herein should be taken as references to quantities of the hydrochloride mono hydrate (HCl. H_2O) form. However, it should be appreciated that the invention extends to other forms, including all pharmaceutically active salts and hydrates thereof.

The term refreshed as used herein may be substituted by any term selected from alert, invigorated, revitalised, re-energised, recharged, rejuvenated, attentive, awake or words having the like effect or equivalent general meaning and the term refreshedness may also be substituted by the grammatical equivalent thereof from the words aforesaid. In addition, the term alert as used herein can be substituted by any of the above alternative terms.

Examples of tablet formulations which may be used in the invention are as follows:

Example 1 – 5mg Tablet

Ingredients	Parts by weight / mg per tablet

1	Triprolidine hydrochloride BP	5
2	Microcrystalline cellulose 102	87.5
3	Lactose	137.5
4	Magnesium stearate BP	1
5	Croscarmellose sodium	25
6	Opaspray White M-1-7111B	1.08
7	French chalk for tablets	0.65
8	Hydroxypropylmethylcellulose 2910 USP 606	3.27

Method

(a) Triprolidine hydrochloride (1) was mixed with approximately one-half of the components (2)-(5) and thoroughly mixed. The remainder of components (2)-(5) were added and mixing continued to achieve uniform distribution of the active ingredient in the mixture.

(b) The mixture was compressed to form tablets, each containing 5mg of active ingredient, in a tablet forming machine.

(c) The tablets were film-coated by spraying with an aqueous suspension of components (6)-(8) containing 15% solids while being tumbled, followed by drying.

Example 2 – 2.5mg Tablet

	Ingredients	Parts by weight / mg per tablet
1	Triprolidine hydrochloride BP	2.5
2	Microcrystalline cellulose 102	87.5
3	Lactose	137.5
4	Magnesium stearate BP	1
5	Croscarmellose sodium	25
6	Opaspray White M-1-7111B	1.08
7	French chalk for tablets	0.65

8	Hydroxypropylmethylcellulose 2910 USP 606	3.27

Method

Prepared by a method analogous to Example 1.

Example 3

Example 3 was produced in accordance with the following composition and constituted the trial formulation unless otherwise mentioned hereinafter. Patients received one tablet for the 2.5mg dose and two tablets for the 5.0mg dose.

	Name of Ingredient	mg/tablet
1.	Triprolidine HCl. H_2O	2.5
2.	Micro-crystalline Cellulose	29.0
3.	Lactose H_2O	60.0
4.	Magnesium Stearate	1.0
5.	Croscarmellose Sodium	10.0

Method

Example 3 was prepared by the method analogous to example 1 (a) and (b) above.

Example 4

Example 4 was produced in accordance with the following composition and method and provides an example of an alternative fast melt formulation.

Triprolidine Fast Melt Tablets (2.5mg)

Ingredient	Functionality	%w/v
Triprolidine Hydrochloride	Active	2.5mg
Mannitol	Filler/sweetener	400mg
Sodium Croscarmellose	Disintegrant	25mg
Aspartame	Sweetener	20mg

Precipitated Silica	Flow aid	10mg
Flavour	Flavour	qs
Magnesium Stearate	Lubricant	2.5mg
Total		460mg

Blend the triprolidine, manitol, aspartame, sodium croscarmellose, silica and flavouring for 20 minutes in a suitable blender. Add the magnesium stearate and further blend for 5 mins. Compress the blend into tablets of weight 460mg.

Examples 5-7 illustrate further formulations for the triprolidine of the present invention.

Example 5

Triprolidine Sugar Free Syrup (2.5mg/5ml)

Ingredient	**Functionality**	**%w/v**
Triprolidine Hydrochloride	Active	0.05g
Purified Water	Solubilizer	50%
Natrosol 250 HX	Thickener	0.6
Glycerin	Sugar free diluent	20%
Lycasin 80/55	Sugar free diluent	20%
Acesulfame K	Sweetener	0.075
Domiphen Bromide	Preservative	0.01
Flavour	Flavour	qs
Colour	Colour	qs
Purified Water to		100%

Dissolve the triprolidine in purified water in a suitable vessel. Stir until a clear solution is produced. In a separate vessel add the glycerin and the lycasin, heat to 40°C. Slowly add the Natrosol. Recirculate through an in-line Silverson ® with a 2mm screen until all the lumps have disappeared and the bulk is uniform.

Add the Natrosol solution to the triprolidine solution via the in-line Silverson ®. Add with stirring the Domiphen Bromide, Acesulfame K, flavour and Colour. Stir until a homogenous mix is produced and pass through a 60 mesh sieve into bulk containers.

Example 6

Triprolidine Hot Drink (2.5mg/sachet)

Ingredient	Functionality	mg/sachet
Triprolidine Hydrochloride	Active	2.5
Acesulfame Pottasium	Sweetener	12.5
Aspartame	Sweetener	12.5
Malted milk Flavour	Flavour	200
French Vanilla Flavour	Flavour	225
Lactose	Filler	2547.5
Purified Water	Granulating solution	qs
Total		3000mg

The triprolidine is dissolved in purified water. Lactose, aspartame and acesulfame are sieved and dry mixed before being granulated with the previously prepared triprolidine solution. The granules are fluid bed dried, sieved and blended with the flavours.

Example 7

Triprolidine Pastille (2.5mg)

Ingredient	Functionality	mg/pastille
Triprolidine hydrochloride	Active	2.5
Gum Arabic	Natural gum	986
Maltitol syrup	sugar free diluent	859.5
Glycerin	sugar free diluent	81
Citric Acid	pH adjuster/flavour enhancer	39

Flavour	Flavour	23
Acesulfame K	Sweetener	2
Hibiscus Extract	Flavour	4
Miglyol Oil – 866	surfactant	4
Water		299
Total		2300mg

The gum is dispersed in water (95°C), with stirring. Maltitol syrup and glycerin are mixed and pumped in to the pre-cooker at 126°C. The gum solution is pumped into the maltitol syrup solution and mixed. The triprolidine, flavours and colours are added to the mixture.

The pastille mixture is pumped from the dispenser to the depositing hopper to form the pastilles in the starch mould boards. The pastilles are left to gel for 6-8 days.

Clinical Trial

The efficacy of triprolidine in enabling a patient to feel refreshed or alert upon waking after taking triprolidine prior to sleeptime was investigated using patients with a history of sleep disorders and utilising triprolidine prepared in accordance with example 3.

The study herein utilised the following determination methods:-

(a) Karolinska scale as defined in: Int. J. Neuroscience 52 29-37 (1990); and
- validation: Sleep 17 (3) 236-41 (1994)

(b) Loughborough Sleep log as defined in : Sleep 17 (2) 146-159 (1994); and
Sleep 18 (2) 127-134 (1995)

(c) Actimetry – AW4 actimeters (Cambridge Neurotechnology) were worn continuously throughout the study. A button was pressed at night when the

subject desired to go to sleep and again in the morning upon waking. The results of the actimeter study were analysed in the manner defined by Horne et al (Sleep, 17(2); 146-159).

SDI% was calculated as follows:-

$$SDI = \frac{\text{Number of 30 second epochs with movement}}{\text{Number of 30 second epochs from total time spent in bed}} \times 100$$

This is the measure of:

1. The length of time it took to fall asleep
2. Any awakenings throughout the sleep period

Expressed as a % of total time spent in bed.

Study Objectives

- To evaluate the effects of two doses of triprolidine compared with placebo.

Study Design

A multiple-dose, placebo-controlled, parallel-group, double-blind, randomised study investigating the effects of 2.5mg and 5mg triprolidine in patients with temporary sleep disturbance.

Male and Female candidates aged 18 years and above were recruited to one of five research centres by means of local advertising. Candidates were screened by means of a telephone questionnaire and selected candidates invited for interview at the research centre. Key inclusion criteria used to select candidates for the study were:

- A record of poor sleep at least 2 nights per week
- A record of poor sleep for at least 1 week but not more than 3 months
- Sleep disturbance not caused by underlying disease
- No excess use of alcohol or drugs
- Sleep disturbance affected daytime functioning

The candidates came to the research centre on Thursday or Friday and were fitted with a wrist actimeter (AW4 from Cambridge Technology) to establish a baseline measure for SDI and were provided with diary cards to record subjective assessments for the Loughborough Sleep Log and the Karolinska Sleepiness Scale. They returned to the investigational site on the Monday and were issued with the study compositions (2.5mg triprolidine, 5mg triprolidine or placebo). The investigator telephoned a central randomisation centre where the subject was randomised to a particular treatment group using a dynamic balanced randomisation algorithm. The subject was given three doses of their allocated study medication and instructed to take a single dose of two tablets 20 minutes before they intended to go to sleep on three consecutive evenings, commencing that evening. The diary cards for the Loughborough Sleep Log and Karolinska Sleepiness Scale were asked to be completed on waking.

The candidates returned to the research centre on the following Friday.

Parameters Evaluated

Candidates were required to complete a questionnaire 15 minutes after awaking on the feeling of refreshedness assessed on a 5-point scale, the Loughborough sleep log.

A daytime sleepiness assessment was also made 20 minutes, 2 hours and 4 hours after awaking on the Karolinska 9-point scale, ie. the sleepiness scale.

Results

198 candidates completed the study, of whom 178 provided evaluable data. (61 placebo, 60 on 2.5mg triprolidine and 57 on 5mg triprolidine. The subjects on 2.5mg dose took one tablet and placebo those on 5mg dose took 2x2.5mg tablets. The subjects on placebo took a dose to match the active treatments (2 tablets).

Key results were as follows:

- There was evidence that there was a lack of daytime sleepiness associated with those patients who took either dose of triprolidine

- The SDI was reduced for both treatments as compared with placebo on every treatment night
- The sleep latency onset was reduced for both treatments as compared with placebo on every treatment night

The following results were obtained for patients taking 2.5mg triprolidine. For the mean of the 3 nights:

- 15 minutes after waking, patients taking triprolidine recorded feeling more refreshed than those on placebo, as determined by the Loughborough sleep log($p < 0.05$).
- There were a greater percentage of people on 2.5mg triprolidine who, on waking were feeling alert, very alert or extremely alert than those on placebo as measured by the Karolinska log.
- There was a lower percentage of people on 2.5mg triprolidine who, on waking were feeling sleepy, and needing to make some effort or very sleepy, needing to make a great effort to keep awake than those on placebo as measured by the Karolinska log.
- There was no evidence of residual hangover effects / morning grogginess from the drug.
- The SDI was significantly reduced compared to those on placebo ($p<0.01$).
- The sleep latency onset was reduced as compared to those on placebo ($p<0.05$).

Further analyses show the advantageous effects of triprolidine in relation to the degree of refreshedness on waking.

The study design used 3 groups. On average, the number of individuals in each of the 3 groups (placebo, 2.5mg triprolidine and 5mg triprolidine) was 60 ± 10 patients.

In the trial, patients were tested during a seven day period and the results have been analysed for a mean of three days in the middle of this period. The effects of triprolidine at dose level 2.5mg and 5.0mg are compared with placebo in table 1.

Table 1

Datasets (a) to (g) – Main Analyses

		Placebo	2.5mg	5mg
(a) SDI (%)		Mean	Mean	Mean
(Sleep latency onset and	Mon	13.19	11.33	11.72
Quality of sleep)	Tues	14.58	12.15	12.71
(Actimeter)	Wed	14.46	11.2	11.81
	Mean of 3	14.26	11.56	12.23
(b)TTSO (min)		Mean	Mean	Mean
(Time to Sleep onset)	Mon	20.75	16.22	16.16
(Actimeter)	Tues	22.29	15.62	17.88
	Wed	20.26	14.8	16.36
	Mean of 3	22.16	15.53	16.93
(c) 15mins after awaking		Mean	Mean	Mean
(1- very refreshed	Mon	3.41	3.33	3.72
5- very tired)	Tues	3.46	3.23	3.56
(Loughborough sleep log)	Wed	3.42	3.18	3.54
	Mean of 3	3.45	3.24	3.59
(d) last night I slept		Mean	Mean	Mean
1- extremely well,	Mon	3.2	2.67	2.49

		Placebo	2.5mg	5mg
5- extremely badly)	Tues	3.06	2.71	2.93
(Loughborough sleep log)	Wed	3.02	2.81	2.64
	Mean of 3	3.11	2.73	2.69
(e) time to fall asleep (min)		Mean	Mean	Mean
(Loughborough sleep log)	Mon	33.61	23.67	22.02
	Tues	29.73	24.44	32.08
	Wed	28.35	20.95	24.24
	Mean of 3	30.98	23.93	26.5
(f) no of times woke up		Mean	Mean	Mean
(Loughborough sleep log)	Mon	1.9	1.18	1.49
	Tues	1.61	1.37	1.42
	Wed	1.43	1.11	1.39
	Mean of 3	1.71	1.22	1.42

Statistical Analysis

Generally the treatment groups were well balanced in terms of the demographic data. Unless otherwise mentioned all group data was analysed using ANOVA. In two cases, namely, how the patient felt 15 minutes after awakening in the Loughborough Sleep Log and the Karolinska Sleepiness Scale at 20 minutes, the two variables were analysed using ANCOVA by including the weekend and the mean of Friday/Saturday/Sunday night as a covariate. The method was a closed test procedure (Williams' test). Each of the tests were to be conducted at the 5% level. The analysis of the secondary endpoints was similarly conducted using the Student's t-tests on parameter estimates taken from the analysis of variance model presented above.

The following is a copy of the "Loughborough sleep log questionnaire" which was used by patients in the study and provided the data for datasets a and b in table 1.

"Loughborough Sleep Log" Questionnaire

This will be completed 15 minutes after waking.

Bedtime Log

I went to bed at : ..... I turned out the lights at : .....

The windows are : shut .....

Not shut .....

Morning Log

I woke up at ..... this morning I got out of bed at ..... this morning

15 minutes after waking I felt :		Last night I slept :	
a) very refreshed		a) extremely well	
b) refreshed		b) very well	
c) neither refreshed nor tired		c) fairly well	
d) tired		d) rather badly	
e) very tired		e) extremely badly	

Night Diary

During the night the windows were left : opened .....

shut .....

During the night the secondary glazing was left : opened .....

shut .....

During the night my partner slept in : the same bed as me .....

a different bed to me .....

As far as I can remember, it took me ..... minutes to fall asleep last night

As far as I can remember, I woke up ..... times last night

Please note the details of any awakenings you can remember in the table below.

Time Length of time awake (mins) Reason for awakening."

Table 2 shows additional data in connection with data set (a) showing the improvement in refreshed responses at the 2.5mg dosage of triprolidine hydrochloride monohydrate.

Table 2

Loughborough Sleep Log: Awoke Very Refreshed or Refreshed Responses

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	N	%	n	%	n	%
Placebo	10	15.2	10	16.4	11	18.3
2.5mg TRP.HCl.H_2O	14	23	14	23	16	25.8
5mg TRP.HCl.H_2O	7	11.5	5	8.2	9	14.8

Similarly, table 3 shows corresponding additional data in connection with data set (b).

Table 3

Loughborough Sleep Log: Last Night I Slept Extremely Well or Very Well Responses

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	N	%	n	%	n	%
Placebo	11	18	12	22.2	13	24.1
2.5mg TRP.HCl.H_2O	24	41.4	23	41.8	22	37.9
5mg TRP.HCl.H_2O	30	50.9	17	28.8	24	39.3

Karolinska's sleepiness scale is set out below and the results for placebo, 2.5 and 5.0mg doses of triprolidine are shown in tables 4 and 5. Table 4 relates to the number of individuals experiencing scales 1, 2 or 3 on the Karolinska scale and table 5 relates to the number of individuals experiencing scales 8 and 9.

Karolinska Sleepiness Scale

This will be completed 20 minutes after awakening and then at 2 hours and 4 hours following the first assessment on days 5, 6, 7 and 8.

1. Extremely alert
2. Very alert
3. Alert
4. Rather alert
5. Neither sleepy or alert
6. Some signs of sleepiness
7. Sleepy but no effort to keep awake
8. Sleepy, some effort to keep awake
9. Very sleepy, Great effort to stay awake, fighting sleep

Table 4

Karolinska 9-point scale

(a) I feel extremely alert, very alert or alert

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	n	%	n	%	n	%
Placebo	9	13.6	14	23.0	11	17.2
2.5mg TRP.HCl.H_2O	13	21.3	13	21.3	13	21.0
5mg TRP.HCl.H_2O	4	6.3	6	9.5	11	17.5

Table 5

(b) I feel (i) sleepy, [and need to make] some effort or (ii) very sleepy, a great effort to keep awake

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	n	%	n	%	n	%
Placebo	8	12.1	10	16.4	9	14.1
2.5mg TRP.HCl.H_2O	7	11.5	8	13.1	4	6.5
5mg TRP.HCl.H_2O	8	12.5	11	17.5	8	12.7

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

Claims

1. The use of triprolidine or a salt or hydrate thereof as active ingredient of an aid to waking refreshed after sleeping.

2. The use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a composition for enabling an individual to wake refreshed after sleeping.

3. The use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for enabling an individual to wake refreshed after sleeping.

4. The use of triprolidine or a salt or hydrate thereof in the preparation of a sleep aid which also enables an individual to wake refreshed after sleeping.

5. The use of triprolidine or a salt or hydrate thereof as active ingredient of a sleep aid which also enables an individual to wake refreshed after sleeping.

6. The use of triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for the treatment or prevention of a sleep disorder which also enables an individual to wake refreshed after sleeping.

7. Use of triprolidine as active ingredient in the manufacture of a composition for the treatment of sleep disorders.

8. The use of triprolidine as active ingredient in the manufacture of a composition for inducing, prolonging and/or enhancing sleep and/or sleep quality.

9. A method for the treatment or prevention of grogginess, drowsiness or lethargy on waking from sleep in a mammal comprising the administration to the mammal in need thereof of a non-toxic effective dose of triprolidine or a salt or hydrate thereof prior to the desired sleeping time.

10. A method for enabling an individual to wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

11. A method for aiding an individual's sleep and for also enabling the individual to subsequently wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

12. A method of treating sleep of a person suffering from a sleep disorder, which method comprises administration of an effective dose of triprolidine as active ingredient to such a person.

13. A method for inducing, prolonging and/or enhancing sleep, which method comprises administration of an effective dose of triprolidine as active ingredient to a person desirous of achieving sleep.

14. A waking refreshed aid comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

15. A pharmaceutical formulation for the treatment or prevention of grogginess, drowsiness or lethargy on waking after sleeping, comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

16. A pharmaceutical formulation for enabling an individual to wake more refreshed after sleeping, comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

17. The use as claimed in any of claims 1-8, wherein the dose of triprolidine administered to the user prior to sleeptime is between 0.01mg and 20mg.

18. The use as claimed in any of claims 1-8, wherein the dose of triprolidine administered to the user before sleeptime is up to 20mg.

19. The method as claimed in any of claims 9-13, wherein the dose of active ingredient of triprolidine administered is between 0.01 and 20mg.

20. The method as claimed in any of claims 9-13 wherein the dose of active ingredient of triprolidine administered is up to 20mg.

21. The pharmaceutical formulation as claimed in any of claims 15 or 16, wherein the instructions for administration instruct a single dose of the active ingredient of triprolidine of up to 20mg prior to sleeptime.

22. The pharmaceutical formulation as claimed in any of claims 15 or 16, wherein the instructions for administration instruct a single dose of the active ingredient of triprolidine of between 0.01 and 20mg prior to sleeptime.

23. A waking refreshed aid as claimed in claim 14, wherein the instructions for administration instruct a single dose of the active ingredient of up to 20mg prior to sleeptime.

24. A waking refreshed aid as claimed in claim 14, wherein the instructions for administration instruct a single dose of the active ingredient of triprolidine of between 0.01 and 20mg prior to sleeptime.

25. A method as claimed in any of claims 9-13, 19 or 20, wherein the triprolidine is in the form of triprolidine hydrochloride.

26. A method as claimed in any of claims 9-13, 19, 20 or 25, wherein the person is suffering from a sleep disorder.

27. A method as claimed in any of claims 9-13, 19, 20 or 25, wherein the person is not suffering from a sleep disorder but is desirous of achieving a feeling of waking refreshed upon waking.

28. A method as claimed in any of claims 9-13, 19, 20 or 25-27, wherein the active ingredient is administered orally, nasally, optically, rectally, pulmonarily, transdermally or sub-lingually.

29. A method as claimed in claim 9-13, 19, 20 or 25-28, wherein the active ingredient is administered in the form of a tablet, capsule, drink, lozenge, drops, emulsion, dry powder, suspension, pastille, patch, suppository, syrup, sub-lingual spray or nasal spray.

30. A method as claimed in any one of claims 9-13, 19, 20, 25-27, wherein the active ingredient is administered to the mucous membranes of the nasal cavity.

31. A method as claimed in any of Claims 9-13, 19, 20 or 25-30, wherein the active ingredient is administered as a solution or suspension spray or as a powder.

32. A method as claimed in any of claims 9-13, 19, 20 or 25-31 in which the active ingredient is administered between 1 minute and 2 hours prior to sleeptime.

33. Use as claimed in any of claims 1-8, 17 or 18, wherein the triprolidine is in the form of triprolidine hydrochloride.

34. Use as claimed in any one of Claims 1-8, 17, 18 or 33, wherein the composition is for oral administration.

35. Use as claimed in any of claims 1-8, 17, 18, 33 or 34, wherein the composition is in the form of a tablet, capsule, drink, lozenge, drops, emulsion, dry powder, suspension, pastille, patch, suppository, syrup, sub-lingual spray or nasal spray.

36. Use as claimed in any one of Claims1-8, 17, 18 or 33, wherein the composition is for administration to the mucous membranes of the nasal cavity.

37. Use as claimed in any of Claims 1-8, 17, 18 or 33, 34 or 36, wherein the composition is a solution or suspension or a powder.

38. The use as claimed in any of claims 1-8, 17, 18, 33, 34 or 36 , wherein the triprolidine forms the active ingredient of a formulation which contains a blend of two or more diluents, one of which may also serve as a disintegrant.

39. The use as claimed in any of claims 1-8, 17, 18, 33, 34 or 36 or 38 , wherein the triprolidine forms the active ingredient of a formulation, which comprises a saccharide diluent.

40. The use as claimed in claim 39, wherein the triprolidine formulation further comprises a disintegrant.

41. The use as claimed in claim 40, wherein the triprolidine formulation further comprises the saccharide diluent and the disintegrant in the ratio of 1-10 parts by weight saccharide diluent to 1 part by weight of disintegrant.

42. The use as claimed in claim 40 or Claim 41, wherein the saccharide diluent is lactose, and the disintegrant is croscarmellose sodium.

43. The use as claimed in any one of Claims 38 to 42, wherein the triprolidine formulation further comprises a lubricant.

44. The use as claimed in claim 43, wherein the lubricant is magnesium stearate.

45. The use as claimed in any one of Claims 38 to 44, wherein the triprolidine formulation is formed with a coating of a hydrophilic polymer.

46. The use as claimed in claim 45, wherein the hydrophilic polymer is a methylated cellulose derivative.

47. The use as claimed in any one of Claims 38 to 46, which is free of ingredients intended or effective to sustain or prolong release of the active ingredient.

48. A method of manufacturing a formulation as claimed in any one of Claims 38 to 47, which involves direct compression of the ingredients into a tablet without an intermediate granulation stage.

49. The uses of triprolidine as hereinbefore described and with reference to the examples.

50. The methods for the treatment of grogginess as hereinbefore described and with reference to the examples.

51. The tablets as hereinbefore described and with reference to the examples.

52. The pharmaceutical formulations as hereinbefore described and with reference to the examples.

53. The waking refreshed aids as hereinbefore described and with reference to the examples.

54. The method for enabling an individual to wake refreshed after sleeping as hereinbefore described and with reference to the examples.

55. A waking refreshed aid as hereinbefore described and with reference to the examples.

56. A pharmaceutical formulation as hereinbefore described and with reference to the examples.

57. Use of triprolidine as active ingredient in the manufacture of a composition for the treatment of sleep disorders as hereinbefore described and with reference to the examples.

58. The use of triprolidine as active ingredient in the manufacture of a composition for inducing, prolonging and/or enhancing sleep as hereinbefore described and with reference to the examples.

59. A method of treating sleep of a person suffering from a sleep disorder, which method comprises administration of an effective dose of triprolidine as active ingredient to such a person as hereinbefore described and with reference to the examples.

60. A method for inducing, prolonging and/or enhancing sleep, which method comprises administration of an effective dose of triprolidine as active ingredient to a person desirous of achieving sleep as hereinbefore described and with reference to the examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/05427

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4439 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, MEDLINE, CHEM ABS Data, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NICHOLSON A N ET AL: "HISTAMINERGIC SYSTEMS AND SLEEP STUDIES IN MAN WITH H1 AND H2 ANTAGONISTS" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 24, no. 3, March 1985 (1985-03), pages 245-250, XP009007027 ISSN: 0028-3908 cited in the application abstract; tables 4-6 --- -/--	1-60

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2003	15/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MONTI J M ET AL: "HISTAMINE H1 RECEPTOR ANTAGONISTS IN THE TREATMENT OF INSOMNIA IS THERE A RATIONAL BASIS FOR USE?" CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 13, no. 2, February 2000 (2000-02), pages 87-96, XP009007023 ISSN: 1172-7047 page 93, left-hand column, line 27-31 ---	1-60
A	COREY J P ET AL: "NASAL CONGESTION: A REVIEW OF ITS ETIOLOGY, EVALUATION, AND TREATMENT" BAR, NOSE, AND THROAT JOURNAL, IPG, CLEVELAND, OH, US, vol. 79, no. 9, September 2000 (2000-09), pages 690-693,696,698,700,702, XP009007022 ISSN: 0145-5613 page 693 -page 696 ---	1-60
P,A	BUYSE B: "INDICATIES VOOR POLYSOMNOGRAFIE" TIJDSCHRIFT VOOR GENEESKUNDE, LEUVEN, BE, vol. 58, no. 16, 15 August 2002 (2002-08-15), pages 1055-1066, XP009007021 ISSN: 0371-683X the whole document -----	1-60

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05427

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1, 5, 9-13, 19, 20, 25-32, 50, 54, 59 and 60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.